PB86-118288

Drinking Water Criteria Document for Silver (Final Draft)

(U.S.) Environmental Protection Agency
Cincinnati, OH

Mar 85

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

FINAL DRAFT
ECAO-CIN-026
March, 1985
EPA-600/X-85-040-

PB86-118288

EPA

Research and Development

DRINKING WATER CRITERIA DOCUMENT FOR SILVER

Prepared for

OFFICE OF DRINKING WATER

Prepared by

Environmental Criteria and
Assessment Office
Cincinnati OH 45268

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TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1.	2.
3. RECIPIENT'S ACCESSION NO. PB86 118288/AS	
SUBTITLE Drinking Water Criteria Document for Silver	5. REPORT DATE 3/85
	6. PERFORMING ORGANIZATION CODE
AUTHOR(S) Environmental Protection Agency	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS U.S. Environmental Protection Agency Office of Drinking Water (WH-550) 401 M St., S.W., Washington, D.C. 20460	13. TYPE OF REPORT AND PERIOD COVERED Scientific review
	14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on silver. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of silver
- Toxicokinetics and human exposure to silver
- Health Effects of silver in humans and animals
- Mechanisms of toxicity of silver
- Quantification of toxicological effects of silver

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Silver properties Silver exposure Silver toxicity Drinking Water		

18. DISTRIBUTION STATEMENT OPEN	19. SECURITY CLASS (This Report) Non-sensitive	21. NO. OF PAGES 97
	20. SECURITY CLASS (This page) Non-sensitive	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DOCUMENT DEVELOPMENT

Linda S. Erdreich, Ph.D., Document Manager
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Authors

Linda S. Erdreich, Ph.D.
Randall F. Bruins, M.S.
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

James Withey, Ph.D.
National Health and Welfare
Ottawa, Canada

Editorial Reviewers

Erma Durden, B.S.
Judith Olsen, B.A.
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Scientific Reviewers

Ernest Foulkes, Ph.D.
Kettering Laboratory
University of Cincinnati
Cincinnati, OH

James Withey, Ph.D.
National Health and Welfare
Ottawa, Canada

Jennifer Orme, M.S.
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Susan Goldhaber, M.P.H.
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC

Document Preparation

Technical Support Services Staff: C. Cooper, P. Daunt, C. Fessler, K. Mann, B. Zwayer, Environmental Criteria and Assessment Office, Cincinnati

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I. SUMMARY

Silver is a white ductile metal which occurs naturally in the earth's crust in pure form and in ores. The monovalent species of silver in natural water may exist as hydrated monovalent anions in compounds with a wide range of solubilities. The concentration of silver in natural waters is extremely low, 0.09-0.55 µg/ℓ, and studies of public drinking water supplies report a median of 0.23 µg/ℓ. Various industries which discharge effluent containing silver include biocide manufacture, photography, porcelain and ink manufacture and electroplating processes. The high cost of the metal encourages recovery.

Silver is absorbed after oral dosing and is distributed systemically. The oral dose is absorbed into the portal circulation passing through the liver prior to the general circulation. Intravenous doses are carried to all internal organs. Dermal absorption occurs through mucous membranes and through broken skin.

Silver has been detected in 50% of samples of 29 human tissues, but at lower levels than other trace elements. Dermal biopsies performed in the 1930's demonstrate that silver accumulates with age: retention in the fifth decade of life was equavalent to 0.1-0.3 g silver. Animal studies of the distribution of radiolabeled silver show silver concentration in the liver and spleen regardless of route of administration and increased doses resulting in greatly increased deposition in liver and spleen.

Silver deposition within internal organs has been studied in rats and mice exposed by ingestion. Histological examination with light and electron

microscopy show silver deposits mainly in basement membranes and phagocytic cells. Silver deposits were never observed in epithelial cells, and deposits did not decrease after animals were restored to tap water. Thus, the reticuloendothelial system is believed to play a major role in silver metabolism.

Silver is deposited in the liver and excreted in the feces, rather than in the urine, regardless of route of exposure or type of silver compound. Cumulative recovery of silver in the feces on the second day after oral exposure was 98 and 99% in the rats and mice respectively and 94% in monkeys. After i.v. dosing recovery of silver was 71, 82 and 44% in those species. Fecal excretion has been observed in humans as well as animals and urinary excretion has not been detected in humans. A study of rats with ligated bile ducts resulted in 19% recovery in feces after 6 days compared to 97% without ligation demonstrating that silver is secreted into the intestine via the bile.

When whole-body activity was assayed in rats and dogs, a three-component experimental curve generally fit the data. Elimination half-times for dogs dosed i.v. were 2.4, 10.4 and 33.6 days. Quantitative data for humans is sparse but shows a qualitative similarity to the kinetic pattern observed in animals.

The acute toxicity of silver to animals consists of effects on the central nervous system including respiratory paralysis. The effect of chronic exposure of animals to silver at levels which do not cause overt toxicity is limited to the characteristic bluish discoloration of the eye and internal organs. This pigmentation, termed argyria, occurs also in human skin as

well as in internal organs, but is not believed to be associated with other adverse health effects.

There are few studies in experimental animals on chronic toxicity of silver. Rats chronically exposed to 63.5 mg/kg silver nitrate in their drinking water develop a pigmentation of the eye which darkens gradually over time as exposure continues. Silver is deposited in the basement membranes of various internal organs, but no adverse health effects occur.

An antagonism between silver and nutritional deficiency of vitamin E and selenium has been demonstrated in rats, pigs and chicks. Liver necrosis which occurs in animals suffering from deficiency of vitamin E and selenium can be more easily induced in animals fed silver. The current hypothesis is that silver induces a selenium deficiency, but the mechanism of the antagonism is not known.

Acute exposures to humans, usually resulting from accidental ingestion, caused corrosive damage to the GI tract leading to shock, convulsions and death. Chronic exposure to low doses had been common up to 1940 because of the varied therapeutic uses of silver compounds. The sole effect related to chronic exposures is argyria, a bluish-metallic discoloration of the skin and mucous membranes which is disfiguring, but not otherwise harmful. Although hundreds of cases are documented as occurring after exposure to silver salts, colloidal silver or the silver proteinate, there is no data on the rate of those effected in a defined exposed population (incidence data). However, dose levels have been reported for many cases of argyria developing after injections of silver arsphenamine for syphilis. This col-

lection of clinical data, including many case reports, suggests a lowest-observed-adverse-effect-level (LOAEL) assuming the argyria to be adverse.

Despite long-standing and frequent therapeutic use of silver, no evidence of cancer in humans has been reported. Injection site and implantation site tumors have been induced with silver in laboratory animals. Results were either negative or included only tumors at the implantation site. Two mutagenicity studies which included silver gave negative results.

Existing guidelines and standards for levels of silver in drinking water are based on the Public Health Drinking Water Standards (1962). This standard was set to protect against argyria and was based on the lowest i.v. dose of silver as silver arsphenamine in a series of cases reported in a review of such cases: this dose was ~1 g. This standard 0.05 mg/ℓ (50 µg/ℓ) was based on the assumption that all ingested silver is absorbed and that amounts ≤1 g will cause argyria. The analysis stated that silver could be ingested at this level for 27 years without exceeding deposition of 1 g. In 1977 the National Academy of Sciences (NAS) reevaluated the stand- ard, assumed 50% absorption and calculated that ingestion over 55 years would result in an accumulation of 1 g. The National Interim Primary Drink- ing Regulations also set the maximum contaminant level at 0.05 mg/ℓ based on the observation that the existing standard had been protective.

It is necessary to reevaluate the existing approaches for the following reasons:

1. The standard appears to be set on one case only and that case was exposed by the i.v. route

2. Retention studies and balance studies in humans suggest that oral absorption is much less than the 50% assumed

3. The current U.S. EPA procedure is to set standards which are protective for lifetime exposures of 70 years; and

4. The standard is described as having a history of protection. However, the absence of argyria attributable to environmental exposures is most likly due to the low level of ambient concentrations.

While some of these points are academic it was deemed necessary to provide an up-to-date risk assessment prior to recommending maximum contaminant levels. Investigation of the literature showed that 1 g of silver, as total dose of silver arsphenamine administered i.v., represented the minimum effective (toxic) dose from many reported cases and was supported by clinical observations that argyria at this total dose is unusual. Furthermore, these cases are exceptional individuals, highly sensitive to the adverse effects of silver because of their disease state and concommitant injections of mercury.

The route of interest for this document is ingestion, therefore an estimate of the fraction retained after oral exposure was necessary. Absorption appears to be balanced by excretion at low ambient levels; animal data range from <1% in mice to 10% in dogs, and one human retention study suggests 18%. Therefore, the oral equivalent of 1 g was recalculated assuming 18% absorption. The total dose was compared to two reported total doses which produced argyria after oral ingestion. These doses were of the same order of magnitude as was the total dose in a study on rats.

An acceptable daily intake (ADI) was calculated on the basis of the estimated total dose which, if ingested over 70 years could cause argyria in sensitive individuals. In the absence of pharmacokinetic data on bioaccumulation, the observed dose in each of 3 cases was used with appropriate uncertainty factors and body weight and prorated over a 70-year lifetime, assuming 2 ℓ of drinking water/day and using the average ADI from these calculations, the calculated AADI is 90 μg/ℓ. If pharmacokinetic data were available to determine the pattern of bioaccumulation the level could be adjusted accordingly.

II. GENERAL INFORMATION AND PROPERTIES

Silver is a rare element occurring in concentrations of ~0.1 ppm in the earth's crust (Weast, 1977). The white, ductile metal occurs naturally in the pure form and in ores. Principal uses of silver are in photographic materials, electroplating, as a conductor, in dental alloys, solder and brazing alloys, paints, jewelry, silverware, coinage and mirror production. Silver is also of some use as an antibacterial agent and has been used in water treatment.

Silver is a transition metal, at. no. 47, at.wt. 107.87. Silver exhibits oxidation states of 0, +1, +2 and +3, but only the 0 and +1 states occur to any extent in the environment. Silver occurs primarily in the form of the sulfide (argentite, Ag_2S) or intimately associated with other metal sulfides, especially those of lead and copper. Other common silver minerals include cerargyrite (AgCl), proustite ($3AgS \cdot As_2S_3$), pyragyrite ($3Ag_2S \cdot Sb_2S_3$), stephanite ($5Ag_2S \cdot Sb_2S_3$) and native metallic silver. Most lead and copper ores are argentiferous, and silver is also commonly associated in nature with gold.

The monovalent species of silver is the form of environmental concern in natural water. Silver may exist in water as simple hydrated monovalent ions completely dissociated from anions that at one time could have been part of its crystalline salt lattice. In addition, monovalent silver ions may exist in various degrees of association with a large number of inorganic ions (e.g., sulfate, bicarbonate and nitrate) to form numerous compounds with a range of solubilities and potentials for hydrolysis or other reactions. Water solubilities of a few common silver salts are: $AgNO_3$, 1220 g/ℓ (0°C); AgCl, 0.89 mg/ℓ (10°C) and AgI, 2.8 µg/ℓ (25°C).

The concentration of silver in natural waters is extremely low, due both to its low crustal abundance and to the effectiveness of controls on its mobility in water. In a study of 10 United States rivers, Kharkar et al. (1968) detected silver in concentrations ranging from 0.092-0.55 µg/ℓ. Hem (1970) cites studies of public drinking water supplies and river waters which report median concentrations of 0.23 and 0.09 µg/ℓ, respectively. Kosarek (1981) reports the detection frequency of silver at 6.6%, with an average level of 2.5 µg/ℓ (evidently an average only of samples where detected), but does not specify the type of water studied. It has been suggested that the amount of free silver present in the aquatic environment is limited by the formation of insoluble silver halide compounds or complexes (e.g., AgCl). In fact, halide precipitation may be important where silver concentrations are elevated (i.e., in industrial effluents), but the low activity of silver in natural waters would seem to preclude any solubility control on its concentration (U.S. EPA, 1979).

Sorption appears to be the dominant mechanism for the partitioning of silver into aquatic sediments. Silver is strongly adsorbed by manganese dioxide, secondarily by iron and less so by various clays. Organic materials also adsorb silver (U.S. EPA, 1979). Silver also is bioconcentrated by aquatic organisms, but not to the same extent as metals such as mercury. Measured steady-state BCFs for silver vary from <1-240 (U.S. EPA, 1980).

Various human practices contribute silver to surface or drinking waters. Silver is discharged to surface waters in effluents of various industries including biocide manufacture, photography, porcelain and ink manufacture, and electroplating processes (Kosarek, 1981). However, the escalating cost

of the metal is spurring development of recovery practices (Rissmann et al., 1981). Certain types of point-of-use water purifiers employ silver as a bactericide and release a silver residual in the effluent (Smith et al., 1977). Elroi (1981) described a process using silver in the treatment of organic wastes, also leaving a residual.

III. TOXICOKINETICS

Absorption

The therapeutic use of silver dates back to the eighth century A.D. and reports of local or generalized bluish discoloration, called argyria, were documented often enough to verify the association with the injection of silver. Reports of occupational and therapeutic argyria as well as studies in experimental animals indicate that silver is absorbed by ingestion and inhalation. Therapeutic use of silver compounds has resulted in dermal absorption through mucous membranes or broken skin. It is not clear whether absorption can occur through intact skin. Quantitative data on the aspects of absorption are available for oral exposure and exposure by injection, but sparse for exposure by inhalation.

Ingestion. Oral uptake of silver is demonstrated but poorly quantified. Hill and Pillsbury (1939) reviewed and analyzed 357 recorded cases of this pigmentation in humans and verified that ingestion of silver compounds may cause argyria.

Quantitative information on the uptake of silver is available from animal studies showing that it is absorbed after oral dosing and distributed systemically. Dequidt et al. (1974) administered colloidal silver orally to Wistar rats using two different dose schedules. The amount recovered, largely from the lungs, liver and kidneys indicated that at least 1-3% of the dose was absorbed. The highest concentration occurred in the lungs at levels almost 6 times that of the liver. This distribution to the lungs is anomalous in comparison to data from other studies and suggests that some of the dose may have been aspirated.

When a small dose (<0.1 μg) of carrier-free radiosilver was administered to rats (not otherwise described) by stomach tube, very little absorption was assumed to have occurred, since 99% of the dose was rapidly eliminated in the feces (Scott and Hamilton, 1950). Uptake which occurred after i.m. and i.v. injections also demonstrated that silver can diffuse across tissue barriers and can be transported by the systemic circulation.

Furchner et al. (1966a,b; 1968) studied the retention of radiolabelled silver compounds administered orally in four species: mice, rats, dogs and monkeys. The protocol is described in Table III-1. Equations were developed which described the temporal relationship of whole body retention. By integrating this function from zero to infinite time an "area under the curve" parameter, which the authors call an equilibrium factor reflecting total body burden and its persistence, was calculated. As Table III-1 shows, these increase in proportion to species size and are greater for i.v. than oral route in all species. The authors concluded that the extent of absorption was in direct proportion to transit time through the gut in these species. Further information on pharmacokinetics was obtained from this data by using a curve fitting procedure, as will be discussed in the section on elimination.

Inhalation. Generalized argyria from occupational exposure to silver nitrate particles in the atmosphere was reported by Harker and Hunter (1935). Six cases were associated with manufacturing and packaging of silver nitrate and silver nitrate products. Hill and Pillsbury (1939) found reports in the literature of cases which occurred in workers in silver mines and workers involved in smelting, polishing and hammering of silver. These

TABLE III-1

Study Protocol and Equilibrium Factor for
Oral and i.v. Administration of ^{110}Silver to Four Species[a]

Species	Strain	Sex	Route	Age (mo.)	Average wt. (g)	Number of Animals	Dose (μ Ci)	Equilibrium Factor[b]
Mice	RF	F	oral	2.8	26.6	12	0.25	0.20
			i.v.	3.1	27.5	12	0.26	1.54
Rats	Spraque-Dawley	M	oral	2.6	355.0	6	0.5	0.41
			i.v.	3.3	415.0	6	0.5	1.78
Monkey	Macaca mulatta	M	oral	≈48	6730	4	0.6	0.52
			i.v.	≈48	6880	4	0.6	4.77
Dog	Beagle	M	oral	90	13330	4	0.6	2.38
			i.v.	78	14400	4	0.4	19.2

[a]Adapted from Furchner et al., 1968

[b]Equilibrium factor = $0.01 \int_0^\infty R_t dt$

where $R_t = \sum_{i=1}^{n} a_i e^{-k_i t}$

and a_i gives the intercept
k is the rate constant
t is time in days

authors considered this to be evidence that silver was absorbed by the pulmonary route and distributed by the systemic circulation.

Uptake from the human lung was documented by a case of an accidental exposure to dust containing ^{110}Ag (Newton and Holmes, 1960). A man who had inhaled dust generated by drilling a hole in a nuclear reactor as part of an experiment was monitored by a whole-body γ-ray spectrometer on the second day and at intervals thereafter up to 200 days. Results indicated widespread activity in the body.

Concerns about the potential radiation hazards of airborne silver prompted an experimental study in which six anesthetized beagles were exposed to metallic silver aerosol consisting of agglomerates with activity median aerodynamic diameters between 0.45 and 0.54 μ (Phalen and Morrow, 1973). The mean deposition of 17% was concentrated in the lower lung region. After 6 hours this accumulation was cleared. The clearance coincided with an increase in deposition of silver in the liver, which indicated uptake from the lung.

Dermal. The comprehensive analysis of the literature on argyria by Hill and Pillsbury (1939) is reported to have included all reported cases of argyria. Pigmentation of the skin was recorded in 357 cases; 28 were localized, but the evidence for absorption through intact skin was not strong. For example, nine of the localized cases occurred in silversmiths where pigmentation was found at the site of injuries from the sharp instruments used in this craft (Harker and Hunter, 1935). The other cases were called "local therapeutic argyria" and resulted from a direct application of a

silver compound to an affected site, suggesting absorption through broken skin. The use of silver for topical treatment had been common since 1850.

An unusual report of localized argyria without evidence of broken skin occurred in a photoprocessor who immersed her hands in an acid fixing bath. Electron microscopy showed that the particles, presumed to contain silver sulfide due to their solubility in sodium cyanide, were sparsely distributed at the dermo-epidermal junction of the papillary bodies adjacent to the sweat ducts (Buckley, 1963; Buckley et al., 1965). The authors concluded that silver had entered through the sweat glands.

Experimental studies have indicated that some absorption may occur through intact skin. Topical application of silver nitrate to the intact skin of 20 guinea pigs resulted in a percutaneous absorption of <1% after 5 hours (Wahlberg, 1965). The shaved skin of 8 or 10 Wistar rats was bathed daily for 3 months with a saturated solution of the colloidal form of silver. The liver, spleen and kidneys contained measurable amounts of silver and traces were found in the heart and lungs (Dequidt, 1974).

One animal study showed that open wounds allow systemic absorption of silver from silver nitrate. Constable et al. (1973) treated open wounds on the backs of guinea pigs with 0.5% silver nitrate solution for 5 days. Silver was found in the skin surrounding the wound and in various organs including the liver and kidney.

The use of silver compounds for antibacterial therapy of burns has led to studies monitoring the therapeutic efficiency of the compounds. The

authors of some of these attempted to measure silver absorption as well. Absorption of silver from silver nitrate and silver sulfadiazine has been demonstrated (Bader, 1977; Burke, 1973; Moncrief, 1974). However, since burn patients in clinical trials are compromised hosts and since absorption from open wounds is not the thrust of this document, further elaboration on these studies is not warranted.

Distribution and Metabolism

The relative amount of silver found in various tissues is determined by the route, the quantity of silver administered and its chemical form. An oral or intragastric dose will be subject to a large "first pass" effect, i.e., a larger fraction of the administered dose will end up in the liver than when silver is administered by any other route. However, once silver reaches the systemic circulation the fraction of the administered dose which is taken up into the systemic circulation will proportion itself to organs and tissues in the same way. The fate, disposition and transport of metallic ions should be considered as a part of the metabolism for metallic species.

Distribution in Human Tissue. Silver is a regular constituent of most human tissues, although it is usually found in lower concentrations than other trace elements. Kehoe et al. (1940) employed spectrochemical methods to analyze trace metal concentrations in tissues of 30 normal American male adults. Minute amounts of silver were found in the blood, brain, liver, lung, rib bone and intestines. No trace of silver was found in urine, kidney, heart, spleen, muscle, long bones and stomach. Tipton and Cook (1963) did spectrographic analysis of 29 tissues of 150 adult subjects in the

United States. Silver was detected in ≈50% of samples of every tissue, generally in concentrations near the lower limit of detection. The median concentration was <10 μg/g tissue ash.

Tipton and Cook (1963) pointed out two problems in comparing reported results from different studies. The first was that different bases of reference exist for reporting concentrations, such as wet, dry and ash weight of the tissues. The second was the lack of an appropriate value for central tendency. When many samples contained concentrations of silver (or other trace elements) below the limits of detection, the distribution of values was not normal. In such cases the mean and standard deviation are not appropriate measures of central tendency.

Biospectrometric analysis of 500 dermal biopsy specimens demonstrated that silver accumulation increased with each decade of life (Gaul and Staud, 1935). The authors concluded that a normal individual in the fifth decade of life has a retention equivalent to 0.1-0.3 g silver.

Distribution in Animal Tissue. Several investigators have studied the distribution of radiolabelled silver to various organs. Gammill et al. (1950) determined that the highest concentration of ^{111}Ag was in the reticuloendothelial system. Colloidal ^{111}Ag was injected in the caudal vein of 10 rats, followed by sequential kill of individual animals. Silver was measured as counts/minute/unit of wet weight, corrected for the natural decay of the radiolabel. On the first day, 92% was recovered with the greatest organ concentration in the spleen followed by the liver, bone marrow, lung, muscle and skin. The largest organ concentration was in the

liver, followed by muscle, bone, spleen, skin and lungs; the feces were not analyzed. Concentrations in the liver and spleen decreased from day 5 through 14. The authors stated that the blood level decreased over time, but no data were presented.

Scott and Hamilton (1950) examined silver disposition in rats after administration by i.v., i.m. and oral routes. They, also, concluded that the reticuloendothelial system plays a major role in silver metabolism. In one phase of the experiment, small amounts (<0.1 mg of carrier-free ^{110}Ag) were injected into the jugular vein of rats. Groups of three rats each were sacrificed at 4 and 16 days postinjection. After 4 days, analysis of silver in 19 organs as percent of dose in each organ showed, in descending order, large intestine, blood, muscle, skin, liver and bone; 94% had been eliminated in the feces. After 16 days only trace amounts of silver remained. A similar pattern of deposition in the blood, liver and intestines was observed after oral and i.m. administration of silver. On the first day after i.m. injection of carrier-free radiosilver, the dose was concentrated in the intestines, blood, liver and kidney.

To assess the difference between this distribution and that obtained after larger doses, Scott and Hamilton (1950) compared groups with 0.1 mg and 1.0 mg (0.4 mg/kg and 4.0 mg/kg) added silver as carrier with a carrier-free group. Animals were assayed in groups of three on day 6 after i.m. injection, and values were corrected for residue at the injection site (i.m. injections were found to give pharmacokinetic data similar to that obtained after i.v. administration). Excretion levels and relative deposition of silver as percent/organ for the three doses are displayed in Table III-2.

TABLE III-2

Deposition of Silver by Dose Level,
6 Days After Intra Muscular Injection[a]

Tissue	Carrier-free (<0.1 μg)	0.1 mg (≃0.4 mg/kg)	1.0 mg (≃4 mg/kg)
	Percent/Organ[b]	Percent/Organ	Percent/Organ
Heart and Lungs	0.06	0.02	0.59
Spleen	0.01	0.13	2.69
Blood	0.50	0.95	3.03
Liver	0.36	2.24	33.73
Kidney	0.07	0.92	0.63
GI tract	1.12	4.22	8.21
Muscle	0.27	0.56	2.39
Bone	0.18	0.35	2.20
Skin	0.24	0.67	7.39
Urine	0.64	0.88	1.82
Feces	96.56	88.95	37.33

[a]Adapted from Scott and Hamilton, 1950

[b]Average percentage of dose in tissues of three rats. Values corrected for recovery and residue remaining at injection site.

Comparison of the low carrier-free dose to that dose with silver carrier added to make it 10 times higher showed relative deposition increased by the following factors: heart and lungs 10, spleen 300, liver 100, blood 6, kidney 8, skeleton 10, muscle 10 and skin 30. This suggests the saturation of some elimination process.

Anghileri (1969) also observed that the relative deposition in various organs was different for ionic radiosilver with carrier from that without carrier (Table III-3). A group of three rats was injected i.v. with ≈10 μg ionic ^{110}Ag as the nitrate alone or with the addition of 20 μg carrier silver. The order of distribution of silver as percent of dose was liver>blood>small intestine>bladder tissue>kidney for each of the doses when the animals were killed 2 hours after exposure. The kidney and bladder had a higher mean concentration as percent of dose/organ in the group without carrier. The liver showed a higher mean concentration in the group with carrier. Standard deviations were presented, but the results were not tested for statistical significance.

Anghileri (1969) interpreted this to mean that a higher fraction of silver will bind to plasma proteins in absence than in presence of carrier. In the presence of carrier silver a greater portion of the silver will remain insoluble, thus is more likely to be trapped by the reticuloendothelial system and excreted through the bile. These results are qualitatively similar to those of Scott and Hamilton (1950). However, quantitative comparisons between the two studies are not possible because of the different doses, carrier amount and time of kill.

TABLE III-3

Relative Organ Concentration by Dose, 2 Hours after Intravenous Injection with ^{110}Silver (three rats/group)[a]

Organ	Carrier-free (≈10 µg) Mean ± Standard Deviation[b]	+20 µg Carrier Mean ± Standard Deviation[b]
Liver	14.7 ± 3.26	21.0 ± 8.56
Kidney	2.88 ± 0.87	0.97 ± 0.18
Small intestine	3.20 ± 0.98	10.7 ± 8.53

[a]Source: Adapted from Anghileri, 1969

[b]Percentage of injected dose/organ

Although silver halides are insoluble in water, Anghileri (1968) found that silver halides are readily broken down in the living organism. He administered an i.v. dose via the tail veins of one group of young albino mice with ^{110}Ag iodide and another group with silver ^{131}I. The amount of silver in the liver was measured at 6 intervals as the mean of three animals/group. The activity remained constant at 53% at 10 minutes to 3 hours but dropped to 44% at 6 hours and 21% at 24 hours.

In a more detailed study Anghileri (1969) injected the tail vein of mice with radioactive silver iodide (^{110}Ag, ^{125}I). Results shown as the mean retention in four mice are displayed in Table III-4 for four organs at 6 intervals. After 24 hours no activity was found in the blood or spleen but by day 7 the liver still showed 10% of the dose. Thus, the liver is again the primary organ of retention, as for other silver compounds.

Dequidt et al. (1974) administered doses equal to a lethal dose of silver nitrate, colloidal silver and silver proteinate i.p. to adult Wistar rats, 8/group. Necropsy of these rats followed by spectrographic analysis for silver showed that for each compound the liver contained the largest concentration of silver. Also, organ concentrations were of the same rank order as the toxicity, (see Table III-5); for example more silver was found in the liver after dosing with the colloid than the nitrate and the least amount with the proteinate.

Furchner et al. (1968) measured retention as a function of time in four species (mouse, rat, dog and monkey) using ^{110}Ag at an unspecified dose, assumed low. (Dose in a previous similar study was 0.4 μCi of ^{110}Ag as

TABLE III-4

Radioactivity Distribution of ^{110}Ag at Different Times After i.v. Injection of Silver Iodide: Four Mice/Group*

	Percent of Dose/Organ					
	10 Minutes	3 Hours	6 Hours	24 Hours	2 Days	7 Days
Blood	19.7±11.5	15.2±8.64	0.02±0.01	0	0	0
Liver	65.6±22.4	40.7±12.6	44.3±12.1	30.9±10.1	20.0±8.24	10.1±6.1
Spleen	0.35±0.11	0.60±0.18	0	0	0	0
Stomach	0.151±0.32	1.25±0.36	0	0	0	0

*Adapted from Anghileri, 1969

TABLE III-5

Distribution of Silver After i.p. Injection of Equitoxic Doses of Three Forms of Silver*

Compound	Amount injected (mg/kg)	Amount of Silver (mg/kg)	Heart	Lungs	Kidney	Spleen	Liver
Colloidal	600.0	420.0	51.0	204.0	134.0	2910.0	22,610.0
Silver nitrate	40.0	25.2	5.4	29.0	67.5	47.0	1,833.0
Silver proteinate	153	11.6	10.0	20.4	16.5	30.0	542.0

*Adapted from Dequidt et al., 1974

the nitrate.) Whole body retention was equivalent by the i.p. and i.v. routes using either the tail vein or the jugular vein for all species. Rats were killed each day in groups of four. When concentrations by organ as percent of dose/g, after i.p. injection were plotted over 22 days, organ retention resembled whole-body retention in all organs (gut, kidney, pelt, lung, liver, blood, carcass, testes) except brain and spleen, which remained high for longer periods of time.

The distribution of silver after inhalation exposure appears to be similar to that observed from the i.v. and i.p. route, due to transfer to the systemic circulation. Newton and Holmes (1966) reported whole-body radioactivity measurements over 600 days after a case of human accidental exposure by the pulmonary route. The first measurements were taken 2 days after exposure. Only 40% of the ^{110}Ag was left 4 days later. Localization measurements taken on day; 2 and 6 generated a profile curve showing widespread distribution. A localized area containing 25% of the activity was believed to be the liver.

Phalen and Morrow (1973) exposed six female beagle dogs to a silver aerosol. Following tracheal intubation the anesthetized dogs were exposed to 10-20 ℓ of air containing metallic silver aerosol of mean aerodynamic diameter ≈0.5μ during a 7-15 minute exposure period. The average deposition was 17%. Scans during the first hour showed activity in the lung, as did a necropsy of one animal. From the pattern of deposition in a dog assayed 6 hours later, it appeared that 90% of the silver absorbed by the lung was carried to the liver by the blood. Silver was also found in the gall bladder, bile and intestines. The accumulation in the liver was more

gradual than with an i.v. dose. The data fit a 3-compartment pharmacokinetic model with initial, intermediate and terminal half-lives of 1.7, 8.4 and 40 days which compares favorably with Furchner (1968) for intravenously injected dogs of 2.4, 10.4 and 33.6 days.

Mechanisms of Transport and Metabolism. The fate, disposition and transport of metallic ions should be considered a part of the metabolism for metallic species. Mechanisms of transport and metabolism can be determined from a variety of investigations. Several studies support the observation that silver is carried in the blood mainly by the globulins and is quickly cleared by the liver, and to a lesser extent by the spleen (Scott and Hamilton, 1950; Furchner et al., 1968). When carrier-free ^{105}Ag was added to the heparinized blood of rats, 64% was associated with the globulin fraction, 16% with albumin and 8% with the hemoglobin (Scott and Hamilton, 1950). Within 5 minutes after radiosilver was injected into rats i.v., 86% was found in the liver. The silver remaining in the blood stream was mainly in the globulin (57%) and albumin (32%). Radioactive ^{110}Ag, as silver iodide, was cleared from the blood of a dog and from rats in 24 hours (Anghileri, 1969).

The pattern of deposition of orally ingested silver in the kidneys of rats and mice was reported in a series of studies designed to assess the formation of glomerular basement membrane under normal and experimental conditions (Walker, 1971; Day et al., 1976; Ham and Tange, 1972; Moffat and Creasy, 1972; Creasey and Moffat, 1973; Danscher, 1981). Functional or toxicological correlates of the phenomenon were not discussed implying that these inert granules were believed to be harmless. These studies can, how-

ever, be used to illustrate tissue deposition of silver. Walker (1971) studied the sequence of silver deposition on kidneys of rats exposed to 1296 mg/ℓ silver as silver nitrate in the drinking water using light and electron microscopy. The main locations of silver deposition were in the basement membranes and phagocytic cells. Silver was not observed in epithelial cells. Within 6 weeks the basement membranes of the glomerulus, colon and liver showed uptake of the labelled silver. After 25 or more weeks the basement membranes of the skin surface, urinary bladder and prostatic acini showed silver deposition. Silver deposition continued in animals restored to tap water for 4 weeks: under electron microscopy increased size of silver granules of the basement membrane was noted.

Several studies of depostion of silver in basement membranes can be used to identify levels of silver which are not associated with observable adverse effects (see Table III-1). In an exploratory study to determine a reasonable nontoxic dose, Walker (1971) observed that rats given 12 millimolar (1296 mg/ℓ) silver as silver nitrate in the drinking water drank less than controls for the first 5 days. They remained healthy for 60 weeks then showed clinical deterioration (not otherwise described) after the 76th week, but returned to normal when regular drinking water was resumed. Silver deposits were detected in the glomerulus by dark field microscopy after 6 weeks. Rats given 6 millimolar (648 mg/ℓ) did not differ from controls and after 12 weeks showed no silver deposits on microscopic examination.

Day et al. (1976) followed the sequence of Ag deposition in mouse glomeruli after exposure to 6 millimolar $AgNO_3$ (648 mg/ℓ) in drinking water by sequentially killing the animals. Using conventional light microscopy,

no morphological abnormalities were observed until glomeruli became darkened at the 14th week. Using electron microscopy, labeling of the basement membrane of capillary loops was observed from the 2nd to 14th week. After mice returned to drinking water without silver, no further changes were observed and labeling did not disappear.

Ham and Tange (1972) observed a continually changing pattern of silver deposition in the glomerular basement membrane of albino hooded rats given 0.25% $AgNO_3$ (270 mg/ℓ) in their drinking water. Granules increased in size as silver intake continued. Silver granules enclosed in vacuoles appeared in axial cells. These increased in size and number as silver disappeared from the basement membrane. Edema was observed in the processes of some epithelial cells. Some abnormalities were noted in glomerular epithelial and endothelial cells compared to control but these were deemed to be neither progressive nor consistent. Silver was never seen in glomular epithelial cells.

A similar pattern of deposition was observed in rat kidneys by Moffat and Creasey (1972). They hypothesized that sites of silver deposition in the rat corresponded to sites at which vessels are permeable to protein. However, the pattern of deposition in the inner medulla of the rabbit differed from that of the rat. In both species deposits occurred mainly in the basement membrane of blood-vessels and the loops of Henle, but distribution in each vessel or loop was asymmetric in the rabbit.

Silver deposits occurred more slowly in immature rats compared to adult rats (Creasey and Moffat, 1973). Silver was first seen by light microscopy

in kidneys of adult rats at 6 weeks and in weanling rats at 12-14 weeks. Granules were smaller and more sparsely distributed in younger rats.

Danscher (1981) developed a histological method to visualize trace silver deposits in tissues based on the reduction of silver ions to metallic silver at the surface of silver grains already in tissue. Silver lactate was injected i.p. into 24 female albino Wistar rats with sacrifice from 30 minutes through 2 months. Control material from uninjected animals was included. Silver was found intra- and extracellularly in lysosomes, fibroblasts, macrophages and bound to reticular and collagen fibers. Silver was found in tissues where it had not been located previously; the motor neurons of the spinal cord, the ovaries and in the fetal liver. The distribution was said to vary with survival time and injected dose, but no supporting data were presented. The goal of the paper was to present the histological method; therefore, all of the areas of silver deposition were not described. Organs in which silver deposition was reported were the kidneys, liver, ovaries, skin, adrenals and pancreas.

Interactions of xenobiotic substances with metallic ions or other endogenous substances is common and often sheds light on mechanisms of action. Silver toxicity was accelerated in laboratory animals which were maintained on diets deficient in vitamin E and selenium. A discussion of the interaction of silver with vitamin E and selenium is found in Section V. Ganther (1950) reviewed these data and suggests that silver induces a deficiency of selenium, making selenium unavailable for synthesis of glutathione peroxidase.

Excretion

The role of the liver in the excretion of silver is fairly clear from the discussion in the sections on distribution and metabolism. Animal studies show a pattern of deposition in liver and other tissues and of fecal rather than urinary excretion, which is qualitatively similar regardless of route or compound. Studies in humans after accidental exposure suggest similar patterns of deposition and excretion. This has been verified by experimental studies in animals where measured doses and sequential analyses have facilitated analysis of temporal relationships for elimination. Pathology studies have identified silver deposits in several tissues, particularly in basement membranes of the kidney.

Whole-body activity was assayed for various time period in four different species (Furchner et al., 1968). Data fitted a function which was the sum of three exponential functions (the number of data points obtained was not given). However, for oral administration to mice and monkeys, which had relatively short followups, two exponential components were found to describe the data adequately. Equilibrium factors (see Table III-1) suggest that the body burden after oral exposure of mice and rats under conditions of chronic exposure would be 6-7 times less than for the same dose given by i.v. routes and in dogs and monkeys 9-10 times less. The relationship between body weight and estimated steady state in animals was extrapolated to a 70 kg mammal to estimate the equilibrium factor for man. By this estimate, the body burden is 2.49 times the daily oral dose.

An excretion pattern with three exponential components was observed in dogs after exposure via inhalation (Phalen and Morrow, 1973). Beagle dogs

were tracheally intubated, exposed to airborne particles generated from the thermal vaporization of radioactive silver wires, and assayed for whole-body radioactivity. Final values for four dogs showed early uptake of silver in blood and high values in the liver probably due to a rate limiting uptake process. The build-up in the liver was more gradual than with an i.v. dose. High levels in blood, liver and bile suggested that 90% of the inhaled silver was removed by transport to the liver by the blood and secreted into the intestine by the bile.

Lung clearance data fitted by a three-component exponential curve after being corrected for isotopic decay, which indicated that a 3-compartment pharmacokinetic model applied. After the initial clearance from the lung, data for clearance from the liver appeared to fit a function having two exponential components.

In a case of exposure of one person to ^{110}Ag dust, Newton and Holmes (1960) monitored whole-body radiation intervals until 200 days after the exposure. Data points were obtained for retention in the whole body and in the liver; ^{110}Ag was also monitored in the excreta. Widespread activity in the body was indicated with 25% of the total radiation concentrated in a location corresponding to the liver. The inhaled silver was eliminated from the body by a kinetic process which followed a biphasic exponential decay curve and which corresponded to a two component model. The effective half-life for the first phase, was ≈1 day and for the slower terminal phase, was 43 days. However, data for the first 2 days was lacking. Early data were obtained by Phalen and Morrow in their study of dogs and fitted to a three compartment model with half-times for the initial, intermediate and terminal phase of 1.7, 8.4 and 40 days.

Rats injected intravenously or intramuscularly with carrier-free radiosilver had elimination curves for silver which showed fecal excretion to be two orders of magnitude greater than urinary excretion through day 60 (Scott and Hamilton, 1950). In these studies, as well as after doses by stomach tube, concentrations in the liver and in the small intestine were initially high and decreased over time, leading the authors to assume that the route of elimination was from the liver through the bile duct to the small intestine. This hypothesis was confirmed by ligating the bile duct of three rats prior to i.m. administration of radiosilver. Table III-6 shows that excretion of absorbed silver was greatly reduced and silver was eliminated much more slowly from the liver than for rats without ligation.

Furchner et al. (1968) described silver retention in four species after dosing via i.v. and oral routes (see Table III-7). In all four species cumulative excretion was greater for oral route. Whole-body retention after oral dosing was described as <1% and <1 week for all species except the dog. The greater amount retained by larger species may have been due to the longer transit time in the G.I. tract.

Klaasen (1979) compared biliary excretion of silver in Sprague-Dawley male rats, New Zealand white male rabbits and mongrel males dogs to compare biliary excretion among species and to determine if excretion went against a concentration gradient. For each of four doses (0.3, 0.1, 0.03, 0.01 mg/kg) administered to groups of 5 or 6 rats the concentration of silver in the bile peaked 30 minutes after administration and then slowly decreased with time over 120 minutes. The concentration in the bile was greater than the plasma in all species with no observable dose gradient. Thus, silver is

TABLE III-6

Deposition of Silver in Tissues After i.m. Injection of Carrier Free Silver in Rats With and Without Ligation of Bile Duct*

Tissue	No Ligation 6 Days After Injection (Percent per Organ)	With Ligation 7 Days After Injection (2 rats) (Percent per Organ)
Heart and Lungs	0.06	0.56
Spleen	0.01	1.29
Blood	0.50	5.96
Liver	0.36	48.31
Kidney	0.07	6.56
GI tract	1.12	2.46
Muscle	0.27	1.53
Bone	0.18	4.07
Skin	0.24	2.27
Urine	0.64	7.96
Feces	96.56	18.78

*Adapted from Scott and Hamliton, 1950

TABLE III-7

Cumulative Excretion in Four Species
After Oral and i.v. Administrations of Silver[a,b]

Species	Route	N	Dose (μ Ci)	Days to Last Count	Cumulative Excretion to Day 2 (%)
Mice	oral	12	0.25	4	99.6
	i.v.[c]	12	0.26	176	82.1
Rats	oral	6	0.5	14	98.4
	i.v.	6	0.5	114	70.7
Monkey	oral	4	0.6	10	94.4
	i.v.	4	0.6	60	44.1
Dogs	oral	4	0.6	137	90.4
	i.v.	4	0.4	142	15.0

[a]Adapted from Furchner, 1968

[b]Strain, sex, age and weight as in Table III-1

[c]Jugular sinus

transported to the bile against a concentration gradient which indicates that active transport and a saturable mechanism is involved.

In rabbits (number not given) the excretion rate was constant over time but 10 times less than for rats. The pattern in dogs was similar but lower than the rate in rabbits. The observation that the species with the lowest rate of biliary excretion (dog) had the highest concentration in the liver suggests that species variation was due to differences in transfer from the liver to the bile. The author concludes that these variations in biliary excretion among animals make it difficult to determine the importance of this excretory route in man.

Anghileri (1969) administered silver to rats by the i.v. route as halides and also observed a decrease in liver concentration over a period of time (see Table III-5). High values of silver in the small intestine 2 hours after injection corroborate the assumption of elimination of silver through the bile.

Dequidt (1974) found low daily levels of urinary excretion after injection with silver nitrate, proteinate or colloid. Doses of 5 mg/silver/kg resulted in daily excretion levels of 2-15 µg/day. The ranges overlapped among the compounds and dosing schedules varied somewhat among the groups.

The low urinary excretion of silver is supported by a few observations in humans. Kehoe et al. (1940) analyzed 24-hour urine samples from 94 normal men of various nationalities, including 30 Americans, and found no silver. The limit of detection was 0.03 mg/ℓ. Radioactive silver was

not detected in the 54 days of urine sampling after a man was exposed to ^{110}Ag dust from a reactor accident (Newton and Holmes, 1966). The limit of detection was 10 pCi. Silver was detected in bulked fecal samples from this individual over a period of 300 days postexposure. Silver in ingested food, in urine and in feces was measured by spectrochemical methods in a woman with severe generalized argyria for three separate 7-day periods to assess excretion of silver (Kent and McCance, 1941). Silver was observed in feces but not in urine, and in each time period more silver was excreted than ingested. However, these small negative balances of ≈1.4 mg/week were believed to be due to desquamation of the silver-containing cells lining the alimentary canal. Clinical observations of cases of arygria invariably show that the condition does not fade. These excretion levels did not have a visible effect on the intensity of the argyria.

Summary

Silver is absorbed from various silver compounds after oral and i.v. dosing, after inhalation exposures, and after dermal exposure of mucous membranes or broken skin. The amount absorbed is ≈10% in all species evaluated and rats dosed intragastrically rapidly excrete 99% of the dose in the feces. A difference in retention between the oral and parenteral routes suggests that silver is subject to a "first pass effect." That is, while an i.v. dose is carried by the systemic circulation to all of the internal organs, an oral dose is absorbed into the portal circulation, passing through the liver prior to entering the general circulation.

Disposition of silver is handled by the reticuloendothelial system and high concentrations are found in the livers of animals and humans after

exposure. Silver has been found in almost every human tissue, although frequently in concentrations so low as to be near the lower limit of detection. In samples where silver was detected, median concentration was <10 μg/g tissue ash. Silver is excreted from the liver into the gastrointestinal (GI) tract as evidenced by the fact that large percentages of the total dose (≈99% in the rat) are recovered in the feces. Urinary excretion exists in animals but accounts for only a small percentage of the total dose and is generally not detected in humans. Biliary excretion is an important excretory mechanism which can lead to enterohepatic recycling and the prolongation of the activity of a dose. Basal membrane deposition and the skin as an excretion route (Buckley et al., 1973) may also represent unusual excretion routes and mechanisms.

Quantitative data on absorption and excretion are available for rats and a few other experimental species, although more detail is available for the i.v. route than for oral exposure. A 3-compartment pharmacokinetic model was fitted to data from dogs dosed i.v. Half-time values were 2.4, 0.4 and 33.6 days compared with values for inhalation exposure of 1.7, 8.4 and 40 days. Data for humans are sparse in quantitative detail but support a qualitative similarity to the pharmacokinetic models observed in animals.

At experimental levels of exposure sufficient to produce argyria, and in human cases of argyria, silver is contained in electron-dense particles in the dermis and basement membrane of the skin and internal organs. These particles have been reported to consist of silver sulfide or silver selenide. The particles have not been found in individuals exposed only to the low ambient levels of silver. The mechanism of formation of the particles is unknown.

IV. HUMAN EXPOSURE

Humans may be exposed to silver in drinking water, food and air. Detailed information concerning the occurrence of and exposure to silver in the environment is presented in another document entitled "Occurrence of Silver in Drinking Water, Food and Air" (Letkiewicz et al., 1984). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

Exposure Estimation

This analysis is limited to drinking water, food and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to silver from sources other than the three considered here. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various silver concentrations. The 70 kg human is used for estimating intake.

Drinking Water. There is very limited data available for characterizing human intake of silver from drinking water provided by public water supplies. Based on the data presented in Letkiewicz et al. (1984), it appears that the drinking water delivered to about half of the ~214 million people in the United States using public water supplies has silver present, at levels in the range of 0.1-10 µg/ℓ, while 10-30% may receive water with levels >30 µg/ℓ. Based on the FRDS data, it can be estimated that ~46,000 people receive drinking water with silver levels >50 µg/ℓ, the current MCL.

The available data are too limited to develop a reliable, detailed profile of human exposure to various levels of silver in drinking water below the current MCL.

Diet. The FDA Market Basket Surveys do not include analysis of silver dietary intake. The ICRP (1974) provided an estimate of silver intake of 70 µg/day for the adult male from food and fluids, indicating that estimates range from 0-220 µg/day. Insufficient details were available to allow an estimate of the proportion of these dietary intake estimates contributed by drinking water.

Respiratory Intake. No information was found specifically addressing respiratory intake of silver. The data presented in Letkiewicz et al. (1984) indicate that reported air levels of silver are generally ~1.0 ng/m³ or less. Using the assumptions of an adult male inhaling 23 m³ of air/day, respiratory intake from exposure to 1.0 ng/m³ would be 0.02 µg/day; the corresponding daily intake on a body weight basis would be 2.9×10^{-4} µg/kg/day, assuming a body weight of 70 kg.

Summary

There is a very limited data base on human exposure to silver from drinking water, food and air. While some information is available to suggest the general range of silver intake from these three media, it is not possible to determine what proportion of the population have drinking water, dietary and respiratory intakes at various levels. For drinking water, it is possible to estimate the size of the population exposed to levels in public water supplies >50 µg/ℓ, the current MCL, but not for various levels at or <50 µg/ℓ. Consequently, a detailed relative source contribution assessment that describes the importance of each medium as a silver source for different segments of the U.S. population could not be developed.

It would appear from the data presented above that for the adult male, air is generally a minor intake source relative to the combined food and fluid intake (0.02 µg/day for air vs. 70 µg/day from food and fluids). The available information does not provide a breakdown of the individual food and drinking water contributions to the 70 µg/day dietary intake estimate. Assuming the 70 kg adult male consumes two 1 day of drinking water, drinking water with silver levels of 10 µg/day (which appears to be the maximum level for ~50% of the public water supplies) would contribute 20 µg/day (0.29 µg/kg/day) to the intake, suggesting that food is the major source for at least half of the adult population. At levels of 30-50 µg/ℓ (which the 1978 CWSS and RWS indicate to be the levels present in ~10-20% of the nation's water supplies), drinking water would contribute 60-100 µg/day (0.86-1.4 µg/kg/day), in which case it would appear to be the predominant source of silver intake.

References

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V. HEALTH EFFECTS IN LABORATORY ANIMALS

General Toxicity

Silver has been used therapeutically for centuries; argyria in humans was reported as early as the 18th century. The extensive use of silver salts in the early part of this century illustrates that it was not perceived to be toxic in prescribed doses. The early but classic text on argyria by Hill and Pillsbury (1939) verifies that while i.v. silver arsphenamine (for syphilis) and mild silver salts were widely used, the single adverse effect noted with therapeutic use was argyria. The response occurred sporadically and was sufficiently rare to permit continued use of silver. Eventually the number of cases occurring in association with the use of silver arsphenamine for syphilis prompted physicians to attempt to establish a dosage which would prevent this condition (Gaul and Staud, 1935). Research in the 20th century on the effects of silver, other than its disinfecting ability, has focused on its metabolism, its interaction with vitamin E and selenium, and its use as an indicator of deposition in basement membrane. Some of these studies help define no-effect levels of silver and levels of silver for toxic endpoints other than argyria. That toxicity has not been observed despite ubiquitous usage probably accounts for the fact that standard toxicity tests have not been performed. Furthermore, individuals with argyria appear to be healthy otherwise.

Acute Exposure. In experiments performed prior to 1900, i.v. administration of high doses of inorganic silver compounds to mammals such as rats, dogs and guinea pigs resulted in effects on the central nervous system including weakness, rigidity of legs, loss of voluntary movement and respiratory paralysis (Hill and Pillsbury, 1939). Injection of silver nitrate has

been known to induce circulatory disturbances, lung edema and congestion. An i.v. dose of a solution of 3.2 mg silver nitrate/kg (2 mg Ag/kg) killed 14 adult dogs in <30 minutes after lung edema, arterial anoxia and a drop in blood pressure (Mazhbich, 1960).

Dequidt et al. (1974) compared the acute toxicity of three pharmaceutically used forms of silver (soluble silver nitrate, colloidal silver and the silver proteinates) in adult Wistar rats. The author stated that in preliminary experiments (not cited) the minimum i.p. dose of silver nitrate resulting in death of the rats within 24-48 hours was 25.2 mg silver/kg. This dose was given to eight rats whose organs were examined for silver at necropsy. A similar lethal effect was induced by the colloidal form following an i.p. dose of 420 mg silver/kg and by the proteinate form at an i.p. dose of 11.6 mg silver/kg. No further details of the experimental design such as other doses used or times of death were given. The reported values show that the colloid is almost 20 times less toxic than the nitrate and the nitrate is half as toxic as the proteinate. Necropsy followed by spectrographic analysis for silver showed organ concentrations for liver, kidney, spleen, lung and heart of the same rank order as the toxicity; for example, 10 times more silver was found in the liver with the colloid than with the nitrate and the least amount with the proteinate.

The single 420 mg/kg dose to rats of silver in silver colloid which caused death in 24 hours by i.p. route did not result in any deaths when administered orally. Mortality was noted only after repeated oral ingestions of 1680 mg/kg daily for 4 days (Dequidt et al., 1974).

Chronic Exposure. Just and Szniolis (1936) reported histological changes in rats receiving drinking water containing 400, 700 and 1000 µg/ℓ of silver. They concluded that water which is disinfected by silver may not be completely harmless. This work is often cited in the literature because it contains descriptions of other experiments designed to determine quantities of silver necessary for disinfection. However, this study of toxicity is flawed and should be disregarded for the following reasons: neither the number of animals, strain nor duration of experiment is given; no control animals are examined histologically; the reported anomalies are described in vague and archaic terms; and the reported accumulation of pigment may well be the deposition of silver granules which is not considered to be associated with any adverse effects.

Olcott (1948) used various concentrations of silver salts to produce experimental argyria. He determined that 1:1000 silver nitrate (635 mg silver/ℓ) in drinking water induced characteristic pigmentation of eye and body organs without shortening the lifespan or affecting the average weights of rats compared to controls. This pigmentation darkened as the treatment continued. Olcott (1947) examined eyes in life and tissue sections at autopsy of 139 rats fed 1:1000 solution of silver nitrate in their drinking water (63.5 mg/kg/d). Rats were observed from weaning until sacrifice or natural death and compared with control rats given water. The pigmentation of the eyes was graded from 1-4. At stage 1, the eyes were slightly gray and at stage 2 they were more gray than pink, at stage 3 very dark but translucent and at stage 4 opaque (Table V-1). While only one dose level was used, several other studies have shown this level to be associated with

TABLE V-1

Experimental Studies of Silver Toxicity: Oral Exposure via Drinking Water

Species Strain	Number	Chemical	Dose Silver	Treatment Duration	Effects	References
Mice (random bred)	18	Silver nitrate 6 mM	65 mg/kg/day	14 weeks	labeling of kidney capillary loops with silver	Day et al., 1976
Rat (Sprague-Dawley)	12	Silver nitrate in distilled water 24 mM	311 mg/kg/day	2 weeks	3/12 died; listless, drinking little	Walker, 1971
Rat (Sprague-Dawley)	12	Silver nitrate 12 mM	129.6 mg/kg/day	76 weeks	clinical deterioration	Walker, 1971
Rat (Sprague-Dawley)	12	Silver nitrate 6 mM	65 mg/kg/day	10 weeks	silver deposits on basement membrane	Walker, 1971
Rats (Norwegian hooded)	9-10/group	Silver acetate 1500 ppm	97 mg/kg/day[a]	50 days	liver necrosis in vitamin E deficient animals; Normal liver with vitamin E supplement	Diplock et al., 1967
Rats (Holtzman)	10/group	Sodium acetate 751 ppm	76 mg/kg/day[b]	52 days	severely depressed growth with low selenium diet; effect is reduced in presence of selenium	Wagner et al., 1975
Rats (Holtzman)	10/group	Sodium acetate 751 ppm	7.6 mg/kg/day	52 days	no growth depression, no liver necrosis	Wagner et al., 1975
Rats ("purebred")	233 survivors (exposed and controls)	Silver nitrate 1:1000	63.5 mg/kg/day	Lifetime (up to 26 weeks)	argyrosis of eyes; no difference in weight from controls; left ventricular hypertrophy ($p<0.01$)	Olcott, 1950
Rats	not given	Silver nitrate 1:1000	63.5 mg/kg/day	218 days	mild arygyrosis; Silver deposition in basement membrane	Olcott, 1948
Rats	98 84 37 5	Silver nitrate 1:1000	3.2 g total 5.7 g total 6.8 g total 9.4 g total	218 days 373 days 447 days 553 days	eyes slightly gray eyes more gray than pink eyes dark but translucent eyes opaque	Olcott, 1947

[a]One group had vitamin E deficient diet

[b]Vitamin E deficient diet; experimental groups with and without selenium supplement

silver deposition in basement membranes but with no adverse health effects (Walker, 1971; Day et al., 1976; Olcott, 1948, 1950). (This information is summarized in Table V-1). The average total dose for stage 1 was given by the authors as 5.0 g silver salt (3.2 g silver). It occurred in 98 animals at an average of 218 days. Histological sections showed few but definite granules in the membranes of Bruch at stage 1. At stage 4 the membrane was almost uniformly black. Thus, there was good correlation between *in vivo* observations and histological endpoints. Findings in the eyes and other organs at autopsy conformed to the pattern found in human autopsies.

Olcott (1948) also autopsied rats which had ingested silver solutions as drinking water (63.5 mg/kg/d). A definite hypertrophy of the left ventricle was frequently found at necropsy. The greatest deposition of silver pigment was found in the basement membrane of the glomeruli. It was then hypothesized that the left ventricular hypertrophy indicated hypertension which may have been related to the weakened basement membranes in the kidney.

Subsequently he compared left ventricular hypertrophy in purebred rats >9 months of age given a 1:1000 dilution of silver nitrate in drinking water and in unexposed controls (Olcott, 1950). The outcome, hypertrophy, was defined as a ratio of weight of left ventricle per 100/g body weight $\geq$0.2. At necropsy, rats in either group with diseased lungs were eliminated; 233 remained. Left ventricular hypertrophy was detected in 29% of rats given the silver nitrate compared with 12% of rats given water. This was statistically significant by x^2 test at <0.01. Microscopic examination verified that this increase was not due to silver deposits in the heart. Rats given silver had no more vascular lesions in their kidneys than did controls.

Advanced pigmentation of body organs indicative of argyria was visible on autopsy. Determinations on a few rats in each group suggested that rats given silver had more proteinuria.

These results, while suggestive of toxicity, are inconclusive. No further studies in animals or humans have addressed the issue of functional kidney damage or of hypertension. However, these effects were detected only after onset of argyria, so protection against argyria might be sufficient to prevent other adverse effects.

Synergism/Antagonism

Interactions with Other Nutrients. Several studies have demonstrated that the effects of silver on rats can be counteracted by vitamin E and selenium (Bunyan et al., 1967; Diplock et al., 1968; Grasso et al., 1969; Wagner et al., 1975). These same effects (liver necrosis) can be induced in pigs (Van Fleet, 1976) and chicks (Peterson and Jensen, 1975) which have been fed adequate levels of vitamin E and selenium by the administration of still higher levels of silver.

These nutrition studies give, in addition, some evidence of levels of silver associated with toxic effects in animals consuming adequate diets. Levels of silver in these studies which result in liver necrosis in vitamin E and selenium-deficient animals are usually above those levels which induce argyria-like organ changes after chronic feeding. However, few studies have been found in which the liver was histologically examined after lower levels of silver ingestion.

Diplock et al. (1967) evaluated the relationship between effect of silver in the drinking water on the health of weanling Norwegian hooded rats and various dietary levels of vitamin E and selenium. Dietary liver necrosis is known to be caused by a combined deficiency of vitamin E and selenium. A control group of nine rats fed the basal vitamin E-deficient diet had normal livers when necropsied at the age of 86 days. Two to 4 weeks after 1500 mg/ℓ silver acetate (970 mg silver/ℓ) was added to the drinking water of a group of 9-10 rats fed the basal vitamin E-deficient diet, all died at a mean age of 55 days. Necropsy showed all had liver necrosis. With the addition to the diet of 1.0 ppm selenium, deaths were reduced to 4/9 after a mean of 74 days. When 120 ppm α-tocopherol (vitamin E) was added to the basal diet, all rats had normal livers when autopsied at day 86 (50 days of silver exposure).

Bunyan et al. (1968), extending these experiments, reported that 6 rats fed a vitamin E-deficient diet and 1000 mg/ℓ silver as silver acetate in drinking water showed no liver necrosis (duration not stated). However, when the yeast was omitted so that 8.3% casein was the only protein, thus reducing the selenium content of the diet, liver necrosis was induced at 130 mg/ℓ silver. They reported that 120 mg/ℓ vitamin E gives "complete protection" against 1000 mg/ℓ silver but details of the experiment defining complete protection were not given.

Grasso et al. (1969) reported that there were no differences in the time of appearance and the histology of liver lesions between rats fed silver in diet and those exposed via the drinking water.

Wagner et al. (1975) postulated that the antagonism of silver and selenium is exerted through an effect on the biosynthesis of the selenium containing enzyme glutathione peroxidase (GP). To test the effect of selenium intake on silver toxicity, two levels of silver, 76 and 751 mg/ℓ, and a control (no silver) were administered in drinking water for 52 days. All experimental groups consisted of ten, 21-day-old Holtzman rats, fed a vitamin E-deficient diet. A similar regime was administered to vitamin E-deficient rats which had selenium added to the diet. Silver, at 751 mg/ℓ, severely depressed the growth of rats on the low selenium diet. Selenium addition overcame this deficit completely in the 76 mg/ℓ silver group but not in the 751 mg/ℓ group. Activity of liver glutathione peroxidase in the selenium supplemented group was reduced to 30% of control at 76 mg/ℓ Ag in drinking water and to 4% of control at 751 mg/ℓ. This activity was not reduced at all in erythrocytes and was not detectable in the livers of rats fed the low selenium (0.02 ppm) basal diet.

A second experiment was designed to test the effect of silver on the drinking water of rats fed a diet adequate in vitamin E and selenium upon activity of the enzyme GP. After 15 weeks of ingestion of silver in drinking water at 751 mg/ℓ, GP activity of this group of rats was 5% of the control in the livers, 37% of control in the erythrocytes and 38% of control in kidneys. These results were significant at $p<0.05$ (Duncan's multiple range test).

Ganther (1980), reviewing the literature on this issue, suggested that silver may induce a selenium deficiency which inhibits the synthesis of GP, a selenoprotein, but that the mechanism involved is still unknown. It is

possible that this antagonism is dependent on nutritional status and therefore is related to individual differences in handling of silver and the development of argyria.

Other Effects

Carcinogenicity. Local sarcomas have been induced after subcutaneous (s.c.) implantation of foils and discs of silver and other noble metals. Furst (1979, 1981), however, cited studies showing that even insoluble solids such as smooth ivory and plastic result in local fibrosarcomas and that tin when crumbled will not. He concluded that i.p. and s.c. implants are invalid as indicators of carcinogenicity because a phenomenon called solid-state carcinogenesis may complicate the interpretation of these tumors. It is difficult to interpret these implantation site tumors in laboratory animals in terms of the route of exposure to humans ingestion in the drinking water. Within these guidelines there are two studies given below in which silver induced no carcinogenic response.

An abstract from a German paper by Schmähl and Steinhoff (1960) reports that colloidal silver was injected both i.v. and s.c. into rats. There were tumors in 8 of 26 rats which survived longer than 14 months. In 6 of the 8, the tumor was at the site of the s.c. injection. In 700 untreated rats the rate of spontaneous tumor formation was 1-3%. No vehicle control was reported.

Furst and Schlauder (1977) evaluated silver and gold for carcinogenicity in a study designed to avoid solid-state carcinogenesis. Metal powder was suspended in trioctanoin and injected monthly, i.m., into 50 male and female

Fischer 344 rats per group. The dose was 5 mg each for 5 treatments and 10 mg each for 5 more treatments for a total dose of 75 mg silver. The treatment regimen included an inert material as vehicle control and cadmium as a positive control. Injection site sarcomas were found only in vehicle control (1/50), gold (1/50) and cadmium (30/50). A complete necropsy was performed on all animals. The authors mentioned the existence of spontaneous tumors in Fischer 344 rats but reported only injection site tumors. They concluded that finely divided silver powder injected i.m. does not induce cancer.

Further support for the lack of silver's ability to induce or promote cancer stems from the finding that, despite long standing and frequent usage, there are no reports of cancer associated with silver. In a recent Proceedings of a Workshop/Conference on the Role of Metals in Carcinogenesis (1981) containing 24 articles on animal bioassays, epidemiology, biochemistry, mutagenicity, enhancement and inhibition, silver was not included as a metal of carcinogenic concern.

Mutagenicity. Much of the experimental work on mutagenesis is prompted by the suspected link between mutagenicity and carcinogenicity. Since silver is not generally assumed to be a carcinogen, interest in its mutagenic ability is low. No evidence of mutagenicity was shown in the two studies which included silver.

Demerec et al. (1951) studied the induction of back-mutations from streptomycin dependence to nondependence in Escherichia coli. The bacteria were incubated with six different effective concentrations of silver nitrate

($5x10^{-6}$% to 10^{-5}%) for 3-25 hours. The mutation rate was greater for controls than for treated plates at every concentration except the lowest. Therefore, silver nitrate was considered nonmutagenic.

Nishioka (1975) screened chemical mutagens by a method called rec-assay, which compares differential growth sensitivities to chemicals in wild and in recombination-deficient strains of the bacterium Bacillus subtilis. Chemicals which are more inhibitory for Rec^- than for Rec^+ cells are suspected mutagens, by virtue of their ability to damage DNA. A 0.05 M silver chloride solution was made with the addition of 1 N NaOH. After 24 hours exposure both Rec^+ and Rec^- cultures showed the same degree of inhibition, again indicating a lack of mutagenic effect.

Teratogenicity. Studies of associations between silver and birth defects which appear in the literature usually include silver as one of a group of metals rather than singling silver out for special study.

Silver was among the 54 elements whose salts were tested for toxicity to 4- and 8-day-old chick embryos by Ridgway and Karnofsky (1952), but it was not among the nine elements (Tl, Cr, Pb, Co, B, As, Rh, Ba and Se) whose salts produced abnormalities in embryonic development.

Robkin et al. (1973) determined concentrations of various trace metals in dry human fetal liver tissue by neutron activation analysis. Concentrations for silver in descending order are in 12 anecephalic fetuses (0.75$\pm$0.15 mg/kg), 9 premature infants (0.68$\pm$0.22 mg/kg), 12 fetuses from thera-

peutic abortions (0.23±0.05 mg/kg) and 14 fetuses from spontaneous abortions (0.21±0.05 mg/kg). Statistical analysis consisted of multiple tests performed among these four groups. The concentrations in anecephalic tissue significantly exceeded that in tissues from therapeutic and spontaneous abortions ($P \leq 0.01$). Mercury concentrations exhibited a similar pattern. The age of the tissue groups increased in the order of increasing mercury concentrations, so that the accumulation of mercury with age rather than a teratogenic effect may have accounted for the differences. The authors felt that more data from large sample sizes were needed to decide whether the silver anomaly was due to a teratogenic effect or to accumulation with age.

Summary

Acute exposures of experimental animals to inorganic silver result in effects on the central nervous system. The lethal i.p. dose for rats varies according to the form of silver; the proteinate is more toxic than the soluble nitrate which is more toxic than the colloid. Oral doses to rats are less toxic than i.p. doses.

Chronic exposures of rats to silver by ingestion result in shortened lifespan or growth depression. Rats show pigmentation of the eyes after lifetime exposure to 63.5 mg/silver/kg/day but no other adverse effects are reported. At this level silver is deposited in the basment membranes of various organs after a few weeks of exposure. Liver necrosis appears with high exposure levels or after exposure of vitamin E-deficient animals. Interaction also occurs with selenium: the effects of silver on rats can be counteracted by vitamin E and selenium.

Subcutaneous implantation of silver has resulted only in sarcomas but injected silver powder does not induce cancer. Silver is not considered mutagenic nor teratogenic. The few studies performed had negative results.

VI. HEALTH EFFECTS IN HUMANS

Throughout the years of extensive therapeutic use of inorganic silver salts and colloidal silver the sole adverse effect reported was argyria. Medical use of silver in the United States declined drastically since 1939, probably due to the development of antibiotics. Consequently, reports of argyria and studies of silver metabolism have declined. The few cases reported are a result of excessive use of self-administered topical silver nitrate or silver protein compounds. There are no epidemiologic studies and no human experimental studies which give data to estimate percent response at various doses. Clinical case reports show attempts to determine the amount of silver which could be administered as silver arsphenamine for syphilis without causing argyria.

Acute Exposure

Although silver compounds had been utilized medically to treat various diseases for centuries, evidence of toxicity was rarely encountered in ordinary clinical practice (Hill and Pillsbury, 1939). After complete analysis of all the literature up to that time, these authors concluded that acute toxicity or death is induced only after ingestion of large doses of silver nitrate accidentally or with suicidal intent. The symptoms, which result from corrosive damage to the gastrointestinal tract, include abdominal pain, diarrhea and vomiting leading to shock and convulsions. Hill and Pillsbury estimate the fatal dose to be 10 g or more of silver nitrate, but recoveries had been reported after larger doses.

Chronic Exposure

Argyria -- Description and Occurrence. Argyria is a striking change in skin pigmentation in which the skin appears blue-grey with a metallic sheen. This discoloration is permanent and darkens in areas exposed to light, consequently it is usually observed first on the skin of the face. In early stages it can be observed in the conjunctiva or in the nail beds. Discoloration can be seen as well in mucous membranes of the mouth and pharynx, in the lips and in many internal organs. It has been reported to occur in people of all ages with time elapsed from initial exposures varying from <1-12 years.

After reviewing the material on 357 recorded cases of argyria and descriptions of autopsies describing the sites of deposition of silver in various organs, Hill and Pillsbury (1939) emphasize: "The ordinary clinical use of colloidal silver compounds practically never gives rise to any gross untoward effect other than argyria." The cases reported in the literature which they reviewed included three in the 18th century, increasing over time to a high rate of about nine per year reported from 1931-1939. Table VI-1 shows the categories, chemicals and routes involved. Most reports discuss 1-4 cases which were ascertained clinically due to the argyria rather than by exposure. The sole exception is the report of industrial argyria which described the occupational exposures of workers who had developed argyria after working as silversmiths or in factories making silver nitrate (Harker and Hunter, 1935).

Dose-Response Estimates. Gaul and Staud (1935) reviewed 70 reported cases of generalized argyria of iatrogenic origin in an attempt to establish

TABLE VI-1

Analysis of 357 Recorded Cases
of Pigmentation of the Skin due to Silver[a]

Category	Number	Chemical or Source	Routes[b]
Generalized therapeutic argyria	220	Silver nitrate, colloidal silver	Oral, nasal, spray or topical
	19	Silver arsphenamine	i.v.
Local therapeutic argyria	17	Silver nitrate, colloidal silver	Local or topical injected
Therapeutic argyrosis (localized pigmentation of the eye)[c]	61	Varied	Instilled into eye
Local industrial argyrosis	14	Polishers, photographers, other silver workers	Dermal possible
Generalized industrial argyria	17	Silversmiths, silver nitrate workers	Oral inhalation and dermal possible
Local industrial argyria	9	Silversmiths, silver nitrate workers	Oral inhalation and dermal possible

[a]Hill and Pillsbury, 1939

[b]Quantitative data are presented in Table VII-2 for oral exposure and in Table VII-3 for i.v. exposure

[c]The authors suggest that this may be the first objective sign of generalized argyria.

safe dose levels. A lack of uniformity in the amount of silver dosage was particularly noticeable in cases of i.v. administration of silver arsphenamine. Table VI-2 shows that discoloration occurred in some patients after injection of 4 or 5 g but in others only after injection of silver arsphenamine 10-20 g. Gaul and Staud (1935) suggested 8 g of silver arsphenamine as a safe total dose which would not generally produce argyria. They note that other authors suggest safe total doses of 12 or 15 g, based on clinical experience. Gaul and Staud (1935) analyzed biospectrograms from individuals representative of successive decades of life to support the hypothesis that existing silver retention accounts for the appearance of argyria after low doses. The density of the silver line was reported to be directly proportional to decade of life.

Hill and Pillsbury (1939) also attempted to determine the minimal amount of silver which produced argyria. Of the 19 reported cases of argyria which occurred after i.v. injection of silver arsphenamine (14.5% silver) to treat syphilis, 4 occurred at total doses below 10 g. Details of these are summarized in Table VI-3. Although dose estimations after time has elapsed presented some difficulty, the smallest total dose which produced argyria by this route was 6.3 g, corresponding to 0.91 g metallic silver. Several factors which complicate this evaluation include the compromised host, the probability of previous exposure to silver in therapeutic doses for a variety of conditions and documented treatment with mercury, bismuth or arsphenamine. (Bismuth and arsenic are known to affect skin pigmentation.) There are no data available to determine relationship of dose to body weight.

TABLE VI-2

Dosage for i.v. Silver Arphenamine Therapy Resulting in Generalized Argyria[a]

Age	Duration of Treatments (Years)	Number of Injections	Total Dose (g)	Dose per Injection
54	2	31	4.1[b]	0.13
64	3.8	40	7.3	0.18
23	3	38	7.6	0.20
61	3	40	8.3	0.21
49	2	34	10.2	0.30
55	4	68	10.9	0.16
53	4.7	100	15.6	0.16
52	9.7	82	16.4	0.20
53	4	60	16.5	0.28
39	2	57	17.1	0.31
37	2.8	43	20	0.47

[a]Adapted from Gaul and Staud, 1935

[b]Original article, (Spiegel, 1931), suggested that argyria was suspected after 5.1 g and confirmed after 6.3 g.

TABLE VI-3

Generalized Argyria due to i.v. Injections of ≤10 g Silver arsphenamine: Lowest Doses of the 19 Cases[a]

Sex	Age	Description	Dose (g)	Grams Silver	Known Additional Medication[b]	Reference
F	49	Syphilis, general paresis	10.2	1.5	3.2 g metallic bismuth	Spiegel, 1931
M	61	Syphilis	8.2	1.2	3.2 g metallic bismuth	Gaul and Staud, 1935
F	23	Late congenital, syphilis (secondary anemia)	7.8	1.1	8.4 g metallic bismuth 7.6 g arsphenamine 0.5 g salicylate of mercury	Spiegel, 1931
M	54	Syphilis, tabes dorsalis	6.3	0.9	7.8 g metallic bismuth 10.0 g arsphenamine 1.7 metallic mercury	Spiegel, 1931

[a]Hill and Pillsbury, 1939

[b]Obtained from original reference

Examination of the reports of generalized argyria resulting from ingestion of silver salts led Hill and Pillsbury (1935) to conclude that a minimum total dose of silver nitrate associated with argyria was 6 g, which is equivalent to 3.8 g silver. As they state, the data on dosage is less certain than that for i.v. doses of the colloid form and dose rates are not available. Only 33 of the cases included a measured total dose and the designation of oral exposure. Table VI-4 summarizes 8 cases which had doses below 20 g silver nitrate. Note that the lowest dose was given to a patient with syphilis; all cases involved individuals who were ill and therefore metabolically abnormal. The case reported by Blumberg and Carey (1934), for example, depicted the subject as emaciated with loss of all subcutaneous fat, weighed 32.7 kg, had scaly skin and secondary anemia, possibly aplastic. Her skin was ashen, not blue but spectrographic analysis of tissues revealed characteristic silver lines.

Contemporary studies (post 1960) which report argyria are generally a result of medication administered totally by the patient, thus information on total dose is not attainable. The silver had been administered for gastritis or for minor nasal or oral problems such as gingival erosions (Pariser, 1978; Mehta et al., 1966; Reymond et al., 1980; Marshall and Schneider, 1977; Aaseth et al., 1981) or in the form of antismoking lozenges (East et al., 1980; Shelton and Goulding, 1979). In several instances the goal of the report was to analyze the skin or tissue by electron microscopy (see Chapter VII). These reports give no information on the probability of response at a given dose level. Few studies contain quantitative data on dose, particularly if exposure occurred many years prior to the manifestation.

TABLE VI-4

Doses Reported for Cases of Argyria Resulting From Injestion of <20 g Silver Nitrate - General Therapeutic Argyria*

Sex	Age	Reason	Total Dose	Equivalent Grams Silver
F	33	Gastrointestinal disturbance	10	6.4
M	48	Gastric distress	9	5.7
M	38	Duodenal ulcer	8	5.1
F	34	"Sclerose en plague"	7	4.4
F	46	Multiple sclerosis	6.2	3.9
M	56	Syphilis, tabes	5	3.2
F	40	Stomach ulcer	4.2	2.7
M	--	Syphilis, tabes	2.2	1.4

*Hill and Pillsbury, 1939

The following study is the only one of the contemporary case reports which gives quantitative information.

A 47-year-old female developed blue-grey discoloration of the face and neck but was otherwise normal (East et al., 1980). Histopathology showed silver particles in the dermis. Prior to the onset of the discoloration she had taken an unspecified amount of oral antismoking lozenges which contained 6 mg silver acetate each. The lozenges deposit silver chloride on the buccal mucosa. Total body silver content measured by in vivo neutron activation analysis was 6.4±2 g.

Summary

In the absence of incidence data, these compilations of case reports are presented to aid in identification of dose level at which no adverse effects occur. Individual case reports do not readily permit strict identification of the maximum level of silver which can be ingested with no adverse effects. Quantitative data on doses administered i.v. over several months or a few years show that adverse effects occurred in patients with syphilis after total dose of silver as low as 1 g. There is no evidence that argyria alone is associated with any adverse effects other than the pigmentation.

VII. MECHANISMS OF TOXICITY

The only adverse effect clearly linked to chronic exposure to silver is argyria as discussed in previous sections. This effect is important due to the disfiguration and to the fact that is mimics the the skin discoloration associated with cyanosis. This section addresses what is known of the mechanism of toxicity, which might better be termed mechanism of action since functional impairment is not known to be associated with argyria.

For an element such as silver the fate disposition and transport are considered part of the metabolic process. The mechanism of argyria appears to be a failure of the body to eliminate silver by the normal processes disscussed in Section IV. Very little is known about the transport and excretion of silver, but it can be assumed that normally silver will be bound to proteins and kept in soluble forms. Eventually silver will be excreted into the gastrointestinal tract. Excessive exposure will cause higher concentrations of soluble complexes in the skin and when a certain concentration has been reached silver will be precipitated by the action of light. The mechanism for formation of particles in internal organs is not clear, but it is conceivable that when the capacity to form protein complexes is exceeded, silver may be precipitated by selenium.

Several investigators have studied silver deposition in cases of argyria. Skin biopsies have been obtained and examined by light and electron microscopy and chemical analysis (Pariser, 1978; Reymond et al., 1980; Buckley et al., 1965; Buckley and Terhaar, 1973; Aaseth et al., 1981; Metha

et al., 1966; East et al., 1980). Such studies have shown that in the skin as well as in internal organs silver is contained in electron dense particles in the dermis and at the basement membrane, but not in the epidermis. It has been claimed that silver may migrate from the dermis to the epidermis and form complexes with melanin (Buckley and Terhaar, 1973). Solubility studies of such particles indicated that in the skin they were made up of silver sulphide; in one study this was confirmed by x-ray analysis (Reymond et al., 1980). In the study by Aaseth et al. (1981), similar analysis of a kidney biopsy showed that the particles consisted of silver selenide.

The silver particles in the skin have not been found in people exposured only to ambient levels of silver (Pariser, 1978). Whereas in normal people the biological half-time of silver seems to be relatively short, in a patient with argyria a radioactive oral dose of silver as the acetate showed a long retention time (East et al., 1980). By in vivo neutron activation analysis the total body burden of silver was estimated to be 6400 mg. The amount of silver in the skin in relation to total body burden was estimated to be of the same magnitude as in normal people. About 18% of a dose of 4 mg silver as ^{110m}silver was retained and did not decrease during a 30 week observation period.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Quantification of Toxicological Effects

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking water volume in } \ell\text{/day}} = \text{mg/}\ell$$

where:

NOAEL = no-observed-adverse-effect level
LOAEL = lowest-observed-adverse-effect level
Body weight = 70 kg for adult or 10 kg for child
Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children
Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited

period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1980) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identify a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines (NRC, 1977) for selection of an uncertainty factor, but must be considered, include the following: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen, mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results, and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

Although argyria has no discernible effects other than the dark pigmentation of the skin, it has been assumed to be adverse, probably because of the psychological effect on the afflicted individual (e.g., Marshall and Schneider, 1977). It mimics cyanosis and therefore might add expense and complexity to the differential diagnosis.

Insufficient data exists to calculate a 1-day HA for silver. The available information on acute toxicity consists of data on lethal doses, such as that provided in the Dequidt et al. (1974) study. This information does not provide dose-response data that is needed in the calculation of a HA. In

the calculation of a 10-day HA, it is necessary to use short-term data from which a NOAEL can be determined. For silver, the available data consists of studies of longer-term duration, 10 weeks to lifetime. Thus, a 10-day HA will not be calculated.

Risk assessment to determine an AADI will be formulated using the approach taken for previous assessments in which an ADI of silver is based on total dose apportioned over lifetime. Several studies which can be used to estimate total intake levels are summarized below.

Animal Studies. Subchronic and chronic studies on exposure of rats to 63.5 mg silver/kg in their drinking water resulted in deposition of silver in basement membranes but no other discernible adverse effects on health (see Table V-1). Olcott (1947) reported that rats which ingested silver in the drinking water developed a slight gray discoloration in the eyes after a total dose of 3.2 g. This discoloration grew progressively darker over time as the rats continued to ingest the silver. This precursor of argyrosis can be used to calculate an AADI because it reports a sensitive pre-argyria endpoint in a large number of animals in a well-designed study.

Human Studies. Human cases of argyria and the doses of silver to which they were exposed were summarized by Gaul and Staud (1935) and Hill and Pillsbury (1939). Although there is some overlap of cases between the two reports, they summarize efforts of clinical researchers to identify a safe total dose level of i.v. silver arsphenamine. The advantage of these data is that total dosages and dosing regimes are reported for all cases of argyria and supported by clinical reports of doses which have been given to

many patients without producing argyria. The disadvantage is that there is no study which followed an identified group of patients exposed to silver to determine if they later developed argyria. Therefore, the incidence of argyria (rate of argyria in a defined population) at the various total doses is not known.

Argyria occurred in a minority of cases (4/19) at doses of 0.9-1.5 g silver (see Tables VI-2 and VI-3) administered over a period of 2-3 years as 30-40 i.v. injections. These individuals are likely to have been sensitive because they were in the late stages of syphilis with possible liver damage and concomitant exposure to mercury (as described in Chapter VIII). Furthermore, many other patients received similar dose regimens without developing argyria.

From this data a total dose of 1 g silver i.v., the same as that used in previous risk assessments, can be used to calculate an AADI. Assuming 18% absorption by the oral route, the total oral dose equivalent to 1 g silver administered i.v. would be 5.6 g. This estimate of absorption is obtained from the study by East et al. (1980) in a woman with argyria who was healthy otherwise. Other human data (Tipton et al., 1966) reported that two subjects were in balance after ingestion of low ambient silver levels; therefore, the estimate of 18% by East et al. (1980) may be high and, thus, conservative. Although the elimination kinetics appear to have been well-defined in a number of cases, both from animal studies (Furchner et al., 1968; Phalen and Marrow, 1973) and human exposure (Newton and Holmes, 1966) and the potential for bioaccumulation would appear to be high for repeated daily intake, there is insufficient data to allow an assessment of the steady state retention in the case of humans.

Previous estimates were based on the i.v. data because no data were identified showing graded dose levels of ingested silver in humans. However, there are two case reports available from which the minimum dose which produces early signs of argyria can be approximated (Blumberg and Carey, 1934; East et al., 1980). The advantage of these reports are that the exposure is in humans by the route of interest (ingestion) eliminating levels of uncertainty. The disadvantages are that these reports are of single cases with inadequate documentation of the dose rate.

The total dose by ingestion necessary to cause argyria can be estimated from the case of argyremia (high blood levels of silver) and a gum line of blue-grey pigmentation (Blumberg and Carey, 1934). The authors were able to calculate from the prescribed dosage that the patient, who was undernourished and had gastrointestinal problems, had ingested 6.4 g silver as silver nitrate over a period of 1 year.

The total dose necessary to cause argyria can also be estimated by considering the whole body retention measured in a woman with argyria (East et al., 1980). It is known that argyria occurred after 6 months of using anti-smoking lozenges containing 6 mg silver acetate and that the retention study using a single dose of radiolabelled silver was performed 2 years later. The quantity of lozenges ingested is unknown, particularly since it is not clear whether she continued using lozenges in the 2 years after the discoloration appeared. To estimate conservatively, exposure will be assumed to have occurred over the full 2.5 years. At the time of the retention study body burden was estimated to be 6.4 ± 2 g (East et al., 1980).

Therefore,

$$\frac{6 \text{ months}}{30 \text{ months}} \times 6.4 \text{ g} = 1.3 \text{ g body burden.}$$

Therefore, the argyria of face and neck which appeared after the first 6 months is estimated to result from a body burden of at least 1.3 g silver. Using an oral absorption value of 18% observed in this individual, total dietary intake in the 6-month period is calculated to have been 7.2 g silver (or ~6-7 lozenges/day) assuming no other intake (i.e., 7.2 ÷ 183 day ÷ 6 mg lozenge).

Quantification of Noncarcinogenic Effects

Table VIII-1 summarizes the quantitative data on humans which can be considered for use in calculating an AADI. Although the oral studies are isolated cases, the similarity among the estimates of total dose offers some support for the use of these data. In all cases this level is in excess of ambient exposures because food and water in all instances may have contained silver. These estimates are conservative and occur in sensitive individuals that show an effect level.

The study of rats by Olcott (1947) has the advantage over human data of showing a level at which discoloration of the eyes of albino rats was only slightly visible. This sensitive endpoint, which shall be considered a NOAEL, occurred after chronic exposure (~218 days) to 63 mg silver/kg/day for an average total dose of 3.2 g/rat.

TABLE VIII-1

Summary of Quantitative Human Data on the Relationship of Silver Intake to Argyria

Route	Estimated Total Dose (g silver)	Total Unit Dose (mg/kg)	Daily Intake Level (μg) at LOAEL[c]	Health Status	Endpoint	Reference
i.v.	5.6[a]	80	219	syphilis-late stage	argyria	Gaul and Staud, 1935
Oral	6.4	196[b]	537	malnourished; gastrointestinal disturbances	blue gum-line; argyremia	Blumberg and Carey, 1934
Oral	7.2	123[b]	337	normal	argyria of face and neck	East et al., 1980
Average	6.5	133	364			

[a]Estimated from many case reports

[b]Based on actual body weight

[c]Adjusted to a 70 kg individual and apportioned over a 70-year lifetime. An uncertainty factor of 2 will be used to calculate ADIs based on this LOAEL; present methodology suggests an uncertainty factor of between 1 and 10 (45 FR 79347). Note, the standard 10-fold uncertainty due to intraspecies extrapolation is not used here to estimate these ADIs because the endpoints were determined in sensitive humans.

This estimate is the same order of magnitude as the human total dose, and thus supports the use of human data for calculating the AADI. An AADI could be calculated using the dose level for rats, a body weight conversion and appropriate uncertainty factors according to U.S. EPA guidelines for health assessment (45 FR 79347), but this does not make optimal use of the data because the sensitive endpoint occurred after partial lifetime exposure. There is no established method for adjusting total dose for rats to total dose for humans; a body weight conversion would not resolve the issue of partial lifetime exposure.

The following calculations on data for humans follow the data summarized in Table VIII-1. The first calculation based on the i.v. dose obtained from clinical reports by Spiegel (1931), Gaul and Staud (1935) and Hill and Pillsbury (1939) is:

$$\text{ADI} = 5.6\ \text{g} \times \frac{1}{25{,}550\ \text{day}} \times \frac{1}{2} = 109\ \mu\text{g/day}.$$

The uncertainty factor of 2 is used to estimate an ADI based on the LOAEL associated with 70 years exposure (45 FR 79347). This uncertainty factor was applied for the following reasons: First, a the 10-fold uncertainty factor is usually applied to human data to account for possible sensitive individuals in the general population. However, the studies used in this calculation involved sensitive individuals and thus an uncertainty factor is probably not needed. Second, a 1- to 10-fold uncertainty factor is usually applied to a LOAEL based on effect severity when estimating an ADI in order to drop the LOAEL into the range of a NOAEL. However, an uncertainty factor less than 10 would be sufficiently protective in this instance, because the estimated dose which caused argyria in 2-3 years is being apportioned over a lifetime and the effect (i.e., argyria) is mini-

mally severe. Other estimates of the ADI can be obtained by standardizing the observed body weight to the 70 kg person and apportioning this estimate over 70 year lifetime (25550 days). From the case reported by Blumberg and Carey (1934) this yields:

$$ADI = \frac{6400\ mg}{32.7\ kg} \times 70\ kg \times \frac{1}{25{,}550\ day} \times \frac{1}{2} = 268\ \mu g/day,$$

For the case reported by East et al. (1980) this yields:

$$ADI = \frac{7200\ mg}{58.6\ kg} \times 70\ kg \times \frac{1}{25{,}550\ day} \times \frac{1}{2} = 168\ \mu g/day.$$

The average ADI for these three calculations is ~182 µg/day. These values are not anticipated to cause argyria in those exposed for 70 years.

AADI Calculations

The AADI is based on the average ADI calculated from the estimated total oral dose of silver associated with argyria from human data. This value may be conservative because an estimated dose which caused argyria in 2-3 years is being apportioned over a lifetime of 70 years. However, the data are not sufficient to allow an assessment of steady state retention in humans.

Calculations above shows the average ADI is 182 µg/day. The average ADI is based on data which accounts for silver intake in excess of silver from other sources such as food; therefore, no correction is needed for dietary and inhalation exposures in the estimation of the AADI. The AADI is:

$$AADI = \frac{182\ \mu g}{2\ \ell/day} = 90\ \mu g/\ell,$$

assuming 2 ℓ of drinking water is consumed per day. If pharmacokinetic data were available to indicate that bioaccumulation is not likely to occur at low dose levels, this AADI could be adjusted accordingly.

The basic differences between this health risk evaluation and ones performed previously are summarized in Table VIII-2.

Existing Guidelines, Recommendations and Standards

The basis for the 1962 Public Health Service Drinking Water Standards was a case of argyria after 0.9 g i.v. injection of silver as silver arsphenamine identified in a review (Hill and Pillsbury, 1939). The calculation of this standard assumes that all ingested silver is deposited and that amounts deposited in excess of 1 g will cause argyria in the general population of humans. Based on this assumption, U.S. PHS (1962) concluded that 50 µg/ℓ could be ingested for ≈27 years without exceeding deposition of 1 g. NAS (1977) assumed 50% absorption resulting in an accumulation of intake totaling 1 g in ≈55 years. Current EPA practice is to recommend levels that would be protective of adverse effects after 70 years of exposure (45 FR 79347).

The EPA's Ambient Water Quality Criteria Document (U.S. EPA, 1980a) includes descriptions of studies which report physiological effects of silver in rats at 400 µg/ℓ (kidney hemorrhage) and 500 µg/ℓ (increase in liver weight) via drinking water. Results of these studies at low levels were not of biological significance (U.S. EPA, 1980a). For example, the study by Just and Szniolis (1936) is not scientifically adequate to establish a criterion (see Chapter V for a description of this study). The U.S. EPA, with the guidance of public comments and peer review, adopted the NAS standard of 50 µg/ℓ as the ambient water quality criterion since it has appeared to be effective (U.S. EPA, 1980a,b).

TABLE VIII-2

Comparison of Current and Previous Health Evaluations for Silver in Drinking Water

Agency	Data Base	Route	Assumed Oral Absorption Rate	Level Recommended	Time before Exceeding Minimum Effective Dose[a]
U.S. PHS, 1962	Lowest dose among cases reviewed by Hill and Pillsbury, 1939	i.v.	100%	50 µg/ℓ	27 years
NAS, 1977	As U.S. PHS, 1962	i.v.	50%	50 µg/ℓ	55 years
U.S. EPA, 1980a,b	Retains NAS, 1977 estimate on the basis of proven protection				
U.S. EPA (this document, 1983)	Gaul and Staud, 1935 Blumberg and Carey, 1934 East et al., 1980	i.v. oral oral	18%[b]	90 µg/ℓ	70 years

[a]Minimum effective dose is estimated to be the amount of silver retained equivalent to 1 g of silver i.v. Assumed consumption is 2 ℓ of drinking water/day.

[b]Conservative estimate - however, the potential for bioaccumulation after repeated doses in humans is not known.

Carcinogenic Effects

Silver is not considered to have carcinogenic effects. No evidence of cancer in humans has been reported despite frequent therapeutic use of the compound over the years. In animals, local sarcomas have been induced after implantation of foils and discs of silver. However, the interpretation of these findings have been questioned due to the phenomenon of solid-state carcinogenesis in which even insoluble solids such as plastic have been shown to result in local fibrosarcomas.

Special Considerations and Special Groups at Risk

There is no evidence that silver is an essential element for animals or humans. Studies have shown that the adverse effects of silver on rats can be counteracted by vitamin E and selenium (Bunyan et al., 1967; Diplock et al., 1968).

The role of the liver in silver elimination suggests that individuals with liver conditions or damage be considered as sensitive to silver. Animal studies suggest that deficiencies in vitamin E and in selenium increase the risk of silver toxicity as a result of an antagonism exerted through an effect on the biosynthsis of glutathione peroxidase (see Chapter V). There are no human data which directly support this antagonism. However, history of argyria suggests that sensitive individuals exist because although many of individuals had been exposed to therapeutic doses a relatively few cases of argyria developed.

..ividuals exposed to silver occupationally should be considered to be at a higher risk of argyria than the average population. Silver is used in

production of coins, jewelry and tableware, in photographic processing, in dentistry, and in the manufacture of electrial apparatus, mirrors and various alloys and solders (Friberg et al., 1979).

Summary

In summary, AADI values for silver were calculated based upon noncarcinogenic effects. An AADI of 90 µg/ℓ was determined based upon data from human studies.

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